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REVIEW article

Mucoadhesive buccal films: A patient-centric approach to rapid and efficient drug delivery

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Abstract: Mucoadhesive buccal films are an innovative transmucosal drug delivery system that significantly overcomes the limitations of conventional oral dosage forms, such as extensive first-pass hepatic metabolism and enzymatic drug degradation, by enabling direct systemic absorption through the highly vascularized buccal mucosa. Constructed from carefully selected natural, synthetic, or semi-synthetic polymers and formulated with permeation enhancers, plasticizers, and taste-masking agents, these flexible films can deliver a wide spectrum of drugs, including small molecules, peptides, and proteins, for local or systemic therapeutic action, offering rapid onset, improved bioavailability, and enhanced patient compliance particularly in pediatric, geriatric and emergency settings. Recent advances in polymer science, nanotechnology, and fabrication technologies, such as 3D printing, have expanded their application range, although key challenges remain in maximizing drug payload, large-scale production, and regulatory standardization; ongoing research prioritizes patient-centric innovation in clinical and commercial translation of buccal films as a future pillar of personalized medicine.

Introduction

The oral route remains the most preferred and widely accepted method of drug administration due to its convenience, patient compliance, and cost-effectiveness. However, conventional oral drug delivery systems face significant limitations, including extensive first-pass metabolism, enzymatic degradation in the gastrointestinal tract, variable absorption rates, and poor bioavailability of certain therapeutic agents. These challenges have necessitated alternative drug delivery routes that can bypass hepatic metabolism while maintaining patient acceptability [1, 2]. Transmucosal drug delivery has emerged as an alternative that offers direct systemic absorption through mucosal surfaces, including buccal, sublingual, nasal, vaginal, and rectal routes. Among these, the buccal route has gained considerable attention due to its unique anatomical and physiological characteristics that make it particularly suitable for drug delivery. The buccal mucosa is an attractive site for drug administration; it provides a relatively large surface area, rich vascularization, and direct access to systemic circulation via the internal jugular vein, thereby avoiding first-pass hepatic metabolism [3]. The gastrointestinal tract presents a hostile environment for many drugs, characterized by extreme pH variations, enzymatic degradation, and variable gastric emptying times. Further, drugs absorbed from the GIT must pass through the hepatic portal system before reaching systemic circulation, resulting in

significant first-pass metabolism that can substantially reduce bioavailability. For drugs with extensive first-pass metabolism, such as nitroglycerin, propranolol, and various peptides and proteins, oral administration often results in poor therapeutic outcomes requiring higher doses and consequently increased risk of adverse effects [3-5]. Hepatic first-pass metabolism involves Phase I and Phase II reactions mediated by cytochrome P450 enzymes and other metabolic enzymes. This metabolic barrier is problematic for drugs with high hepatic extraction ratios; thus, a significant portion of the administered dose is metabolized before reaching systemic circulation. Moreover, enzymatic degradation by proteases and peptidases in the GIT makes oral delivery of peptide and protein drugs nearly impossible without extensive formulation modifications [6].

Buccal films, known as mucoadhesive films or buccal patches, represent an innovative pharmaceutical dosage form that combines the advantages of transmucosal delivery with modern film technology. These thin, flexible polymeric films are designed to adhere to the buccal mucosa and release the drug either locally or systemically over a predetermined period. The development of buccal films addresses multiple limitations associated with conventional oral dosage forms while offering several unique advantages, including rapid onset of action, improved bioavailability, and enhanced patient compliance [7]. This review aims to explore buccal films as a patient-centric transmucosal delivery system, covering their anatomical basis, formulation components, preparation methods, characterization techniques, clinical applications, and prospects in personalized and emergency therapeutics [1, 7, 8].

The importance of buccal films in modern pharmaceutical sciences is underscored by their versatility in delivering a wide range of therapeutic agents, including small molecules, peptides, proteins, and even vaccines. Recent advances in polymer science, nanotechnology, and manufacturing techniques have further expanded the potential applications of buccal films, making them suitable for personalized medicine, pediatric and geriatric populations, and emergency medications. The global market for buccal drug delivery systems has witnessed substantial growth, with several products receiving regulatory approval and commercial success, particularly in areas such as pain management, antiemetic therapy, and hormone replacement [8]. Also, buccal films offer unique opportunities for delivering drugs that require rapid therapeutic action, such as in acute pain management, breakthrough cancer pain, migraine, and cardiovascular emergencies. The ability to terminate drug delivery by simply removing the film provides an additional safety advantage, particularly for potent opioid analgesics and other drugs with narrow therapeutic indices. As pharmaceutical research continues to evolve toward patient-centric drug delivery systems, buccal films are positioned to play an increasingly important role in modern therapeutics [9, 10].

The oral cavity is lined by a mucous membrane that varies in structure and function depending on its location. The buccal mucosa, which lines the inner cheeks, is classified as non-keratinized stratified squamous epithelium and is considered one of the most permeable regions within the oral cavity [11]. Understanding the anatomy and physiology of the buccal mucosa is crucial for the rational design of buccal drug delivery systems. The buccal mucosa consists of about 40-50 cell layers with a total thickness of 500 to 800 micrometers. The epithelium itself comprises 100-200 micrometers of this thickness, while the remaining portion consists of the lamina propria and submucosa [12]. The epithelial layer is composed of four distinct strata: stratum basale (basal layer), stratum spinosum (spinous layer), stratum granulosum (granular layer), and stratum superficiale (superficial layer). The basal layer contains proliferating cells that gradually differentiate and migrate toward the surface, which are shed into the oral cavity [5, 13, 14]. The lamina propria, located beneath the epithelium, consists of loose connective tissue rich in blood vessels, lymphatics, and nerve endings. This highly vascularized region is responsible for the rapid systemic absorption of drugs that permeate through the epithelial barrier. The submucosa contains larger blood vessels, glands, and adipose tissue, providing structural support and additional vascular access. The extensive vascular network in the buccal mucosa, comprising the buccal artery branch, ensures efficient drug absorption and rapid onset of therapeutic action [6]. The buccal mucosa maintains a neutral pH ranging from 6.8 to 7.4, which is favorable

for drug stability and permeation. The mucosa is continuously moistened by saliva secreted from major and minor salivary glands, with an average saliva flow rate of 0.5-2.0 mL/min at rest [1]. Saliva contains water, electrolytes, proteins (amylase, lysozyme, and peroxidase), mucins, and immunoglobulins, which influence drug stability, mucoadhesion, and absorption characteristics [15].

Drug molecules can traverse the buccal epithelium through three principal pathways: transcellular (intracellular), paracellular (intercellular), and trans appendageal routes. The predominant pathway depends on the physicochemical properties of the drug molecule, including molecular weight, lipophilicity, charge, and size [2, 11]. Transcellular pathway: This route involves drug transport directly through the epithelial cells. Lipophilic drugs with favorable partition coefficients readily dissolve in the lipid bilayers of cell membranes. The transcellular route requires the drug to cross multiple cell membranes (apical and basolateral membranes of successive cell layers), making it particularly suitable for small, uncharged, lipid-soluble molecules. However, the presence of metabolic enzymes in epithelial cells can degrade drugs traversing this pathway, particularly peptides and proteins [3]. Paracellular pathway: This route involves drug transport through the intercellular spaces between epithelial cells. Small hydrophilic molecules and ions primarily utilize this pathway. The paracellular route is regulated by tight junctions, which are protein complexes that seal the intercellular spaces and maintain epithelial barrier function. While the paracellular pathway occupies only a small fraction of the total epithelial surface area (0.01%-0.1%), it represents an important route for hydrophilic drugs. The permeability of tight junctions can be modulated by permeation enhancers, potentially increasing drug absorption [4]. Trans-appendageal route: This pathway involves drug transport through hair follicles and gland ducts present in the mucosa. Although this route represents a small fraction of the total surface area, it may contribute to the absorption of some macromolecules and delivery systems. The trans-appendageal pathway is considered less significant than transcellular and paracellular routes, but may play a role in the absorption of nanoparticulate drug delivery systems [7].

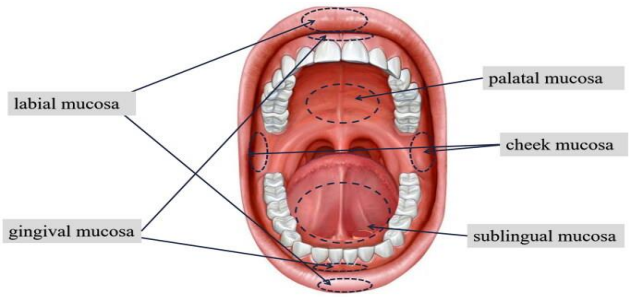


Figure 1: Anatomical regions of the oral mucosa [16]

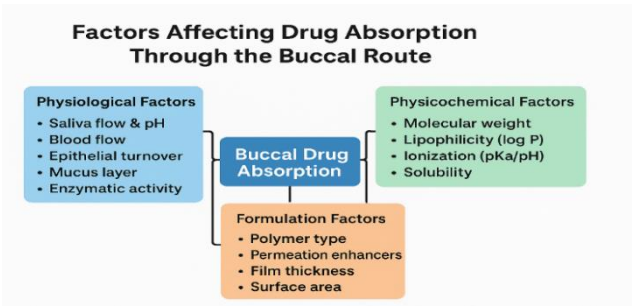


Figure 2: Factors affecting drug absorption [1, 4, 7, 9, 11]

Advantage of buccal films: Buccal films bypass hepatic first-pass metabolism, allowing direct entry of drugs into systemic circulation and improving bioavailability [8]. They protect drugs from degradation caused by gastric pH, digestive enzymes, and intestinal microflora, improving the stability of sensitive molecules [9]. They are thin, flexible, and easy to administer, making them highly acceptable for pediatric and geriatric patients [1]. The rich vascularization of the buccal mucosa enables rapid absorption with a short onset of therapeutic action [7]. Buccal films can be designed for controlled or sustained drug release, maintaining stable plasma concentrations and improving therapeutic outcomes [4]. They allow precise dosing and can be customized in different sizes and strengths according to patient needs [8]. Drug delivery can be immediately stopped by removing the film from the buccal cavity in case of adverse effects or overdose [9]. They exhibit better stability and longer shelf life [11].

Disadvantage of buccal films: The buccal mucosa has a limited surface area, which restricts absorption of drugs demanding high doses [1]. The buccal epithelium acts as a barrier that limits the permeability of large or hydrophilic molecules [4]. Continuous saliva secretion can dilute and wash away the drug, decreasing

bioavailability and therapeutic effect [3]. Films can be unintentionally swallowed during eating or speaking, leading to reduced absorption and first-pass metabolism [7]. Some patients may find the films uncomfortable, especially during eating or talking, which reduces acceptability [9]. Direct contact of drugs and excipients with the oral mucosa may cause bitter taste, irritation, or allergic reactions [8]. Maintaining the mechanical strength, flexibility, and chemical stability of films during storage and handling remains a major challenge [1]. Buccal films can only incorporate a limited amount of drug, making them unsuitable for high-dose formulations [4]. Producing films with uniform thickness and consistent drug content during large-scale manufacturing is difficult [7]. Buccal films face regulatory challenges due to the absence of standardized evaluation and approval guidelines [8].

Table 1: Ideal characteristics of buccal films

Category	Characteristic	Eligibility criteria - description	Ref.
Physicochemical properties	Thickness	50-500 µm; uniform across the surface to ensure comfort and consistent drug release	1, 2
	Surface quality	Smooth, uniform surface free from air bubbles, cracks, or wrinkles; improves appearance and acceptance	9
	Moisture content	3-10%; maintains flexibility and prevents microbial growth or brittleness	17
	pH	Near neutral (6.5-7.4); avoids mucosal irritation and enhances drug stability	2
	Drug content uniformity	±10% of labeled amount; ensures dose consistency and uniform distribution	18
Mechanical and Bio-adhesive properties	Tensile strength	0.5-5 MPa; provides resistance to tearing during handling	19
	Flexibility / Elongation	10-100% elongation; ensures comfort and adaptation to oral movements	7
	Mucoadhesive strength	5-50 g force; maintains adhesion under saliva and tongue motion	9
	Folding endurance	≥300 folds; indicates good flexibility and mechanical durability	20
	Swelling property	Controlled swelling promotes adhesion and drug release without discomfort	13
	Hydration rate	Rapid hydration within 10-60 seconds initiates adhesion and release	2
Patient acceptability factors	Comfort and application	Easy to handle, adheres quickly, and remains comfortable without irritation	1
	Taste and flavor	Pleasant or effectively masked taste enhances compliance	7
	Mucosal safety	Non-irritating, biocompatible excipients prevent mucosal damage	7
	Packaging	Unit-dose, protective, and easy-to-open pouches maintain stability and convenience	21
	Residence time	15 minutes to several hours; ensures complete drug release and therapeutic effect	20
	Removability	Easily removable without residue or mucosal damage	7

Formulation components

Polymers form the base of buccal films, affecting strength, adhesion, and drug release. Natural polymers such as chitosan, alginate, and gelatin offer biodegradability and safety [22]. Synthetic ones; PVA, PVP, PEG, and Carbopol, provide consistent quality and flexibility. Semisynthetic cellulose derivatives, including HPMC, HPC, MC, and EC, are most used for their film-forming ability and controlled release. Combining polymers (HPMC-PVA, chitosan-PVA) improves mechanical strength, mucoadhesion, and drug release. Selecting suitable polymers ensures film uniformity, stability, and patient acceptability [1, 8].

Plasticizers improve flexibility, reduce brittleness, and enhance handling by lowering the polymer's glass transition temperature. Common examples include glycerin, propylene glycol, PEG, triacetin, sorbitol, and

mannitol. They affect film strength, elasticity, and drug release. The optimal concentration (20%-40% w/w polymer) balances flexibility and mechanical integrity, while excessive amounts may cause softness or stickiness. Proper plasticizer-polymer compatibility ensures stability and uniformity. The choice of plasticizer depends on the polymer type, the drug's nature, and desired film properties [8, 9].

Regarding active pharmaceutical ingredient: Drugs suitable for buccal films typically have a molecular weight <500 Da, moderate lipophilicity (log P 1-3), and stability at pH 6.8-7.4. Ideal drugs avoid first-pass metabolism and show potency below 30 mg. Examples include fentanyl, ondansetron, nitroglycerin, estradiol, and insulin. Compatibility with polymers is crucial to prevent drug instability or altered release. Analytical studies such as DSC, FTIR, and XRD confirm drug-polymer compatibility [1, 7].

Permeation enhancers increase mucosal permeability to improve drug absorption. They act by altering lipid bilayers, opening tight junctions, or modifying mucus structure. Common enhancers include surfactants (SDS, Tween 80), bile salts, fatty acids (oleic, capric), EDTA, cyclodextrins, and chitosan. The ideal enhancer is effective at low concentration, reversible, and non-irritating. Overuse may cause mucosal irritation or instability. Optimized combinations often enhance absorption while maintaining safety [8, 9].

Saliva stimulants aid hydration and mucoadhesion. Citric, malic, and ascorbic acids are used at 1.0%-5.0% w/w to enhance saliva flow. Sweeteners improve taste and compliance, especially in pediatric and geriatric patients. Aspartame, sucralose, saccharin, sorbitol, mannitol, and xylitol are widely used. Xylitol offers antimicrobial and cooling effects. Sweetener selection depends on compatibility, sweetness intensity, and patient preference [8, 11].

Flavoring and coloring agents enhance palatability and mask bitterness. Common choices include mint, fruit, and vanilla. Essential oils like peppermint and eucalyptus provide flavor and mild permeation enhancement. Coloring agents improve appearance and product identification; approved dyes (FD & C colors) and natural pigments (turmeric, beet, carotenoids) are used. Titanium dioxide acts as a whitener. Both flavor and color agents must remain stable, safe, and compatible with formulation components [1, 4].

Backing membranes and release modifiers provide unidirectional drug release and protect films from saliva. Common materials include ethyl cellulose, Eudragit RS/RL, and polyethylene. They enhance bioavailability and prevent drug loss. Release modifiers regulate drug diffusion and kinetics. Hydrophobic polymers, pH-dependent materials, and pore-forming agents are used to achieve controlled, sustained, or pulsatile release. Proper selection of these materials ensures desired drug-delivery performance and stability [7, 8].

Methods of preparation of buccal films

Solvent casting is the most commonly used method for preparing buccal films due to its simplicity, scalability, and ability to produce uniform films [1]. In this method, polymers, drugs, and excipients are dissolved or dispersed in a suitable solvent to form a homogeneous solution. The solution is poured onto a leveled casting surface or mold and dried under controlled conditions, resulting in thin films that can be cut to the desired size [7]. Plasticizers, permeation enhancers, and other excipients are incorporated.

Plasticizers, permeation enhancers, and other excipients are incorporated to enhance flexibility and drug release. Careful control of temperature, solvent choice, and drying time is essential to avoid defects or drug degradation [4, 8-11].

Advantages: Simple, cost-effective, and easy to perform, uniform drug distribution and controlled film thickness, suitable for water-soluble and water-insoluble drugs, and scalable from laboratory to industrial production.

Limitations: Long drying times, drug degradation of heat-sensitive drugs, solvent residue concerns, batch-to-batch variation, and environmental and safety issues related to organic solvents.

Table 2: Polymers, plasticizers, and active pharmaceutical ingredients used in buccal film formulations

Polymer	Polymer Name	Plasticizers	API	Ref.
Cellulose derivative	Methyl cellulose	Propylene glycol, PEG-400	Cetylpyridinium chloride	23
	Methyl cellulose	Propylene glycol, PEG-400	Carvedilol	24
	Ethyl cellulose	PEG-400, triethyl citrate, glycerol, dibutyl phthalate	Fluticasone propionate	25
	Ethyl cellulose	Propylene glycol, PEG-800, PEG-600	Propranolol hydrochloride and nifedipine	26
	Hydroxypropyl methyl cellulose	Propylene glycol, PEG-400, glycerol, sorbitol	Glibenclamide	27
	Hydroxypropyl methyl cellulose	PEG-3350, triethanolamine	Lidocaine hydrochloride	28, 29
	Hydroxypropyl cellulose	Propylene glycol, PEG-400, glycerol	Ketorolac tromethamine	30
	Hydroxypropyl cellulose	PEG-3350	Diltiazem hydrochloride	31
	Hydroxyethyl cellulose	PEG-400, triethyl citrate, glycerol	Moxifloxacin hydrochloride and clove Oil	32
	Hydroxyethyl cellulose	Castor oil, propylene glycol	Hyaluronic acid	21
	Carboxymethyl cellulose	PEG-400, propylene glycol, glycerol, sorbitol	Ibuprofen	33
	Carboxymethyl cellulose	Triethyl citrate, PEG-800, triethanolamine	Lysozyme and epidermal growth factor	34
Synthetic	Polycarbophil	Glycerol, PEG-3350, triethanolamine	Propranolol hydrochloride	35
	Poly-ethylene oxide	PEG-3350, glycerol	Domperidone	36
	Poloxamer	Propylene glycol, PEG-600, glycerol	Methylene blue	37
	Polyacrylic acid	Propylene glycol, PEG-800, Glycerol, PEG-400	Atenolol	38
	Polyacrylic acid	Triethanolamine	Prednisolone	39
	Polymethacrylic acid	Propylene glycol, PEG-400, PEG-200	Acyclovir	40
	Polymethacrylic acid	Triethanolamine	Almotriptan	41
	Polyvinyl alcohol	Glycerol, PEG-400, Propylene glycol	Paracetamol	42
	Polyvinyl alcohol	Sorbitol	Dexamethasone	43
	Polyvinyl pyrrolidone	PEG-400, triethyl citrate, glycerol	Simvastatin	44
	Polyvinyl pyrrolidone	PEG-600, castor oil, triethanolamine	Epidermal growth factor and lysozyme	35
	Proloc™ Bio adhesive (PRO)	PEG-400, propylene glycol, PEG-200	Rizatriptan benzoate	45
Natural	Chitosan	PEG-800, dibutyl phthalate	Miconazole nitrate	46
	Gelatin	glycerol	Ondansetron hydrochloride	47
	Gelatin	glycerol	Lidocaine hydrochloride	48
	Sodium alginate	PEG-400, glycerol, propylene glycol	Nicotine	49, 50
	Gellan gum	Glycerol, propylene glycol	Triamcinolone acetonide	51
	Carrageenan	PEG-400, glycerol, PEG-600	Streptomycin and diclofenac	52
	Pectin	PEG-400, glycerol	Metronidazole	53
	Hyaluronic acid	PEG-400, glycerol	Benzydamine hydrochloride	54
	Rice starch	Glycerol, PEG-400, Sorbitol	Diclofenac sodium	55
	Pullulan	Glycerol, propylene glycol	Yonkenafil	56
	Lyocoat™ (Pea Starch) (LYO)	Glycerol	Furosemide	57

Hot-melt extrusion is a solvent-free, continuous technique in which solid polymer, drug, and excipients are melted and mixed in an extruder. The molten mass is forced through a die to form a film, which is cooled and cut into the desired size [59]. This method allows high-throughput production and can improve drug solubility by forming solid dispersions or solutions [8].

Figure 3: Schematic representation of the solvent-casting film system [58]

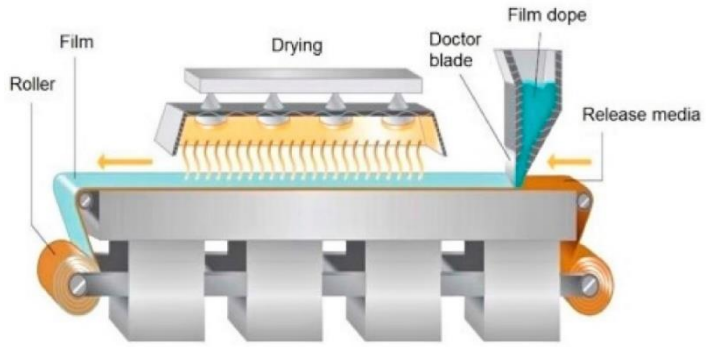
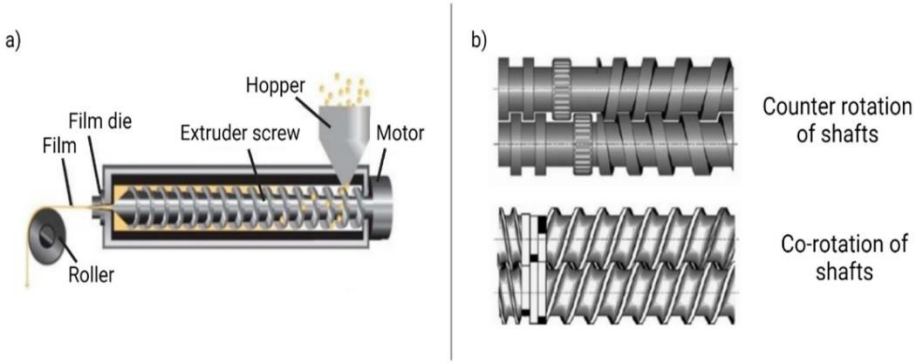


Figure 4: Schematic representation of the film extrusion system [58]



Advantages: Solvent-free, environmentally friendly, continuous production and high throughput, improved content uniformity, reduced processing time compared to solvent casting, and suitable for heat-stable drugs and thermoplastic polymers.

Limitations: Requires heat-stable drugs and excipients; specialized, costly equipment is needed; limited to high drug-load formulations, and polymer selection is limited by thermal and rheological properties.

Direct milling produces fine polymer-drug powders that are compressed into films without solvents or heat, suitable for heat- and solvent-sensitive drugs [11]. Electrospinning forms nanofiber mats with high surface area and porosity, enhancing drug release [8]. Printing technologies, including inkjet, flexographic, and gravure printing, allow precise drug deposition and personalized dosing [60]. Layer-by-layer assembly enables the construction of multilayer films with controlled thickness and drug loading [4]. Freeze-drying produces porous films for improved mucoadhesion and drug release, though it is time-consuming and expensive [7].

Advantages: Suitable for heat- and solvent-sensitive drugs, high surface area and controlled drug release (electrospinning), personalized dosing and precise drug distribution (printing), and multilayer architecture for complex release profiles (layer-by-layer)

Limitations: Difficulty achieving uniform drug distribution (direct milling), complex process optimization (electrospinning, printing), and expensive and time-consuming (freeze-drying)

3D printing enables layer-by-layer fabrication of buccal films using inkjet deposition, extrusion-based printing, or stereolithography (SLA) [8, 60, 61]. This allows personalized dosing, integration of multiple drugs, and creation of complex geometries with tailored drug release.

Advantages: Personalized and on-demand production, precise control over drug distribution and release, integration of multiple drugs and complex structures, and reduced material waste

Limitations: The limited availability of pharmaceutical-grade printable materials, high initial equipment costs, slower production speed compared to conventional methods, and regulatory and stability challenges.

Evaluation and characterization of buccal films

The development of buccal films requires thorough evaluation and characterization to ensure their quality, safety, and therapeutic efficacy. Comprehensive assessment including physical, mechanical, physicochemical, biological, and stability parameters, which collectively determine the performance of the dosage form [1].

Physical evaluation: Physical properties of buccal films are critical to patient acceptability, drug release, and uniformity across batches. Uniformity in thickness affects drug loading, mechanical strength, and comfort during application. Films are typically measured at 5.0-10.0 random points using a digital micrometer. For most formulations, a thickness range of 100 to 500 µm, with acceptable variation of ±5% to 10% [7]. Weight variation to ensure dose consistency. Individual films are weighed using an analytical balance. Ten to twenty films per batch are assessed, with weight variation limits conforming to the Pharmacopeial standards [9]. Non-uniform weights indicate uneven polymer distribution or irregular casting. Folding endurance: Reflects flexibility and resistance to mechanical stress. Standard film strips are repeatedly folded until they break. A folding endurance of ≥300 folds is considered acceptable, with higher values indicating superior mechanical resilience [62]. Films are observed for air bubbles, cracks, surface irregularities, and discoloration. Transparency, color uniformity, and overall appearance are recorded, as defects can impact patient compliance and drug performance [8].

Mechanical properties: Mechanical testing evaluates the strength, flexibility, and durability of films during handling and application. The maximum stress a film can endure before breaking is measured using a texture analyzer or universal testing machine. Tensile strength ranges from 0.5 to 5 MPa depending on polymer composition. Strong films resist tearing during packaging and handling [1, 7]. Percent elongation: Measures the film's ability to stretch before rupture, expressed as a percentage of the original length. Higher elongation indicates flexibility and improved mucosal conformity [9]. Young's modulus: determines the stiffness or elasticity of the film. Calculated from the initial slope of the stress-strain curve, lower values reflect softer, more flexible films, whereas higher values indicate rigidity [63].

Physicochemical evaluation

Surface pH: Critical for avoiding mucosal irritation. Films moistened with distilled water or simulated saliva should exhibit near-neutral pH (6.5 - 7.4) [8].

Moisture content and uptake*:* Moisture impacts stability, mechanical properties, and microbial growth. Karl Fischer titration or loss on drying is used to quantify water content, typically 3.0% - 10.0% w/w. Moisture uptake under controlled humidity assesses environmental stability [4, 7].

Drug-excipient compatibility: Preformulation studies employ DSC, FTIR, XRD, and TLC to detect potential interactions or chemical incompatibilities that could affect drug stability or release [1].

Drug content and uniformity*:* Drug content to ensure therapeutic efficacy. Known-size films are dissolved in suitable solvents, and drug concentration is measured using validated analytical techniques such as UV-Spectrophotometry or HPLC. Ideal drug content ranges between 90.0% - 110% of the labeled dose [9]. Content uniformity: To confirm consistent drug distribution across individual films. Ten randomly selected films are tested, with relative standard deviation (RSD) <6%, and pharmacopeial limits of 85% - 115% of the average content [63].

In vitro studies: Rapidly disintegrating films should dissolve in simulated saliva within seconds to a few minutes. Disintegration is visually observed or tested using the modified USP apparatus [8]. Dissolution studies quantify the rate and extent of drug release. Various USP apparatuses or modified methods, including rotating cylinder and flow-through cell methods, are employed. Typically, ≥80.0% of the drug should be

released within the specified time. Drug release kinetics are analyzed using models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas to understand release mechanisms and optimize formulation [1, 4].

Mucoadhesive strength: Ex vivo testing: Films are applied to excised buccal mucosa, and detachment force is measured. Higher values correlate with prolonged residence time and effective drug delivery. Acceptable mucoadhesive strength ranges from 5.0 to 50.0 g, depending on the formulation [9, 11]. Synthetic membranes or gels provide reproducible models for adhesion testing; shear stress and tensile detachment methods [8].

Ex vivo and in vivo permeation: Ex vivo studies*:* Drug permeation through excised mucosa is measured using Franz diffusion cells. Key parameters include cumulative drug permeation, steady-state flux, permeability coefficient, and lag time [7]. *In vivo* studies: Animal models (rabbits, dogs) provide pharmacokinetic data, including Cmax, Tmax, AUC, and bioavailability. Human studies are required for final validation, safety, efficacy, and therapeutic equivalence [8, 9].

Stability testing: Accelerated and long-term stability: Films are stored under ICH-recommended conditions (40°C/75.0% RH and 25°C/60.0% RH, respectively) and evaluated for physical appearance, drug content, dissolution, mechanical properties, and degradation [1, 7]. Light, temperature, humidity, pH, and oxidative stress predict shelf life and guide packaging decisions [9, 11].

Challenges in buccal drug delivery systems

The development of buccal drug delivery systems continues to face significant scientific, technological, and regulatory challenges despite their potential to improve therapeutic outcomes and patient compliance. One of the primary limitations lies in formulation design, regarding the incorporation of large or poorly soluble molecules. The restricted surface area of mucoadhesive systems inherently limits drug loading capacity, making it difficult to achieve a high drug payload in buccal films. The delivery of macromolecules such as peptides and proteins also presents substantial challenges due to enzymatic degradation, poor permeability, and molecular instability, even though this route shows promise for low-molecular-weight lipophilic drugs. For instance, the delivery of gold glycan-coated nanoparticles embedded with recombinant human insulin using the Pharma Film® system failed to achieve satisfactory buccal bioavailability [2]. Furthermore, the poor solubility of Biopharmaceutics Classification System (BCS) Class II drugs continues to limit bioavailability, necessitating innovative formulations that prolong mucosal contact time and enhance solubility, such as those developed for hyaluronic acid in oral ulcer treatment [21, 64].

Manufacturing challenges have also hindered progress in the large-scale commercialization of buccal films. Although advanced fabrication methods such as 3D printing, particularly Fused Deposition Modeling (FDM), have gained attention, they remain limited by technical and scalability issues [5]. The production of filaments through Hot-Melt Extrusion (HME) requires precise control of processing conditions, while semi-solid extrusion (SSE) drying steps can cause unwanted dimensional changes in printed objects. Consequently, most studies have been confined to laboratory-scale manufacturing with poor reproducibility and limited clinical translation. Additionally, regulatory challenges surrounding the validation and standardization of *in vitro* models hinder both reproducibility and inter-laboratory comparison. The current *in vitro* mucoadhesion and permeation testing methods inadequately represent the complexity of the human buccal mucosa, complicating *in vitro-in vivo* correlation. Variability in mucosal conditions among different patient populations further complicates standardization efforts, limiting regulatory approval and delaying commercialization [5]. Beyond formulation and regulatory challenges, the pharmaceutical industry also faces broader systemic risks that affect buccal film development. Dependence on imported raw materials and excipients exposes manufacturers to supply chain disruptions influenced by international regulations and geopolitical factors, leading to production delays and cost escalations. Furthermore, non-compliance with global regulatory requirements and failed inspections can result in product recalls and financial penalties, significantly impeding innovation and production continuity [65].

Future perspectives and directions

The future of buccal drug delivery studies is designed for personalization, nanotechnology integration, biologic delivery, and regulatory advancement. Personalized medicine represents a paradigm shift toward patient-centric therapy that is customized to individual needs. Technologies such as 3D printing, including HME FDM and inkjet printing, are at the forefront of this movement, enabling the fabrication of tailored multilayered oral films with precise drug distribution [2]. Combining FDM with inkjet printing techniques further enhances design flexibility and facilitates the creation of complex drug-release systems [63]. Nanotechnology-based systems are emerging as a promising solution to overcome payload limitations and improve drug permeation. Incorporating nanoparticles into mucoadhesive polymers allows higher drug loading, better stability, and enhanced mucosal penetration [2]. Functionalized nanoparticles can facilitate targeted drug delivery and improved bioavailability, while mesoporous silica nanoparticles show potential in developing stable amorphous systems for poorly soluble drugs [2, 66]. The buccal delivery of biologics and peptides remains a promising yet underexplored field, with mucoadhesive films potentially serving as effective carriers for these sensitive molecules. Emerging systems such as microneedle-assisted buccal delivery may further enhance macromolecule absorption [2]. Additionally, the expansion of cost-effective buccal film technologies could significantly improve access to essential medicines, especially in developing nations [5]. To advance clinical and commercial translation, researchers are focusing on improving *in vitro* and *in vivo* correlations by dissolution media that simulate human saliva, offering a more physiologically relevant testing environment [5]. Parallel to technological advances, future strategies emphasize integrating proactive quality and risk management approaches in line with ICH Q9 guidelines to ensure product safety, regulatory compliance, and sustainability [65]. The continued evolution of buccal drug delivery systems will thus depend on harmonizing innovation with regulatory readiness and scalable manufacturing, ensuring that these novel formulations achieve their full therapeutic potential.

Conclusion: Mucoadhesive buccal films represent a pivotal advancement in patient-centric drug delivery by offering effective alternatives to traditional oral systems, especially for drugs with poor bioavailability or requiring rapid therapeutic action. Despite current formulation manufacturing and regulatory obstacles, the integration of new technologies such as 3D printing and nanomaterials promises to enhance precision, versatility, and global accessibility of these systems. Continued interdisciplinary research and regulatory alignment are essential for realizing their full potential across diverse clinical settings, ultimately shaping the future of personalized and emergency drug therapy.

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